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(54) Title: A METHOD FOR REDUCING SKIN IRRITATION AND STING FROM WEAK CARBOXYLIC ACID

(57) Abstract: A method for reducing skin irritation and/or sting that may be caused by a weak carboxylic acid by adding polyethylene glycol (PEG). Addition of PEG lowers irritation and sting without reducing the delivery of weak acids to skin tissues.

A METHOD FOR REDUCING SKIN IRRITATION AND STING FROM WEAK CARBOXYLIC ACID

This invention relates to a cosmetic method for reducing skin irritation and sting from weak carboxylic acid by polyethylene glycol.

Cosmetic products which improve the appearance of skin are increasingly popular with consumers. Frequently, consumers seek to alleviate or delay the signs of aged or photo-aged skin, such as fine lines and wrinkles, dry and sagging skin.

Some ingredients used in topical products are potentially irritating, especially to people with "sensitive skin." Such irritation is commonly perceived as sting or burning.

As an example, hydroxy acids and several other weak carboxylic acids have been proven to deliver cosmetic benefits, such as improvement in the appearance of photo--damaged or naturally aged skin, skin lightening, treatment of age spots, etc. Unfortunately, their use at high concentrations may occasionally be associated with skin irritation, e.g. skin redness and stinging sensation upon application. For aesthetic reasons, these actives are most often delivered as oil-in-water emulsions. Practically, the final composition pH should be higher

than 3 in order to prevent deleterious effects to skin tissues and unacceptable levels of irritation. Water soluble weak acids when delivered from an oil-in-water emulsion at acidic pH often induce high levels of sting. The sting occurs immediately after application, reaches a maximum intensity usually by 5-8 minutes after application and then begins to reduce in intensity.

The irritation can be ameliorated by lowering the amount of an active ingredient in the composition or by reducing the active's penetration through the skin. A serious drawback of both approaches is that the efficacy is impaired. The weak acid related irritation can be reduced by raising the composition's pH but this method yields reduced efficacy due to a decreased acid penetration through the skin. It is desirable to reduce or eliminate the irritation potential of weak acids while maintaining their efficacy.

One approach to lower the sting is to formulate the acid with a strong alkali metal base. Yu et al. (U.S. patent 4,105,783) suggested the use of ammonium hydroxide or an organic base. Unfortunately, this method raises the pH of the composition and reduces the ability of the weak acid to penetrate the skin, thus lowering its efficacy *(see Sah et al. in J. Cosmet. Sci. 49, 257-273, 1998)*.

A clear need exists for a cosmetic composition with a weak acid that reduces sting but does not reduce dermal delivery.

Polyethylene glycol has been used in cosmetic compositions, which also contain an alpha hydroxy acid. See for instance US Patent 5,863,943 (Groh et al.) and US Patent 5,411,734 (Vargas et al.). The prior art described above, however, does not disclose the anti-sting or anti-irritant ability of polyethylene glycol.

The invention provides a method for reducing skin irritation caused by the topical application of a composition containing a weak carboxylic acid, the method comprising topically applying polyethylene glycol in a cosmetically acceptable vehicle. The present invention is based, at least on part, on the discovery that polyethylene glycol reduces the sting and/or irritation that may be caused by weak carboxylic acids, without impairing their delivery to the skin.

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts of material or conditions of reaction, physical properties of materials and/or use are to be understood as modified by the word "about." All amounts are by weight of the composition, unless otherwise specified.

The term "skin" as used herein includes the skin on the face, neck, chest, back, arms, armpits, hands and scalp.

The terms "irritation", "sting", and "burn", "inflammation", and "redness" as used herein are synonymous and are used interchangeably.

The molecular weight herein is expressed in Dalton (D). The numerical terms followed by the letters "KD" denoting molecular weight of a compound, to be read as the numerical term x 1,000 e.g. 10KD means molecular weight of 10,000 D)

Polyethylene glycol (PEG) is a water-soluble, thermoplastic polymer produced by the heterogeneous polymerisation of ethylene oxide. The white, free-flowing resins are characterised by the following structural formula: $-(-CH_2\ CH_2O-)_n$. The molecular weight of PEGs suitable for use in the present invention generally ranges from 200 D to several (e.g. five) million D, preferably from 200 D to 20 KD, to maintain anti-irritation efficacy, yet to minimise an increase in formulation viscosity. The amount of polyethylene glycol in the inventive composition ranges from 0.1 to 20%, preferably from 1 to 15%, most preferably from 0.5 to 10%.

A weak carboxylic acid suitable for use in the inventive compositions is an acid with a dissociation constant,

pKa, of above about 2. Preferably, the pKa is above about 3, most preferably in the range of from about 3 to about 5.

An acid is a species having a tendency to lose a proton, while a base is a species having a tendency to accept a proton. Hence for every acid, HA, there is a conjugate base A^-:

$$HA \Leftrightarrow H^+ + A^-$$

Thus, lactic acid-lactate ion is an example of a conjugate acid-base pair.

Acids so defined can only manifest their properties by reacting with bases. In aqueous solutions, acids react with water, the latter acting as a base:

$$HA + H_2O \Leftrightarrow H_3O^+ + A^-$$

Quantitatively, the acid strength of HA, relative to the base strength of water is given by the equilibrium constant expression by the equation:

$$K = [H_3O^+]\,[A^-] / [H_2O]\,[HA]$$

where parentheses denote molar concentrations.

As almost all measurements are made in dilute aqueous solution, the concentration of water remains essentially constant and its activity can be taken as unity. Letting H^+ represent the solvated proton, we have:

$$K_a = [H^+][A^-]/[HA],$$

where K_a is the acidic dissociation (or ionization) constant. This equation can be written in the form:

$$pK_a = pH + \log [HA]/[A^-]$$

where pK_a is the negative logarithm of K_a, and is equal to the pH at which the concentrations of HA and A^- are equal.

The pK_a for alpha hydroxy acids is generally from 2-4, for monocarboxylic acids from 3-5, for alpha amino acids from 2-3; and for salicylic acid it is 3.0.

The pK_a of a weak water-soluble acid is obtained by titrating it with a strong base such as sodium hydroxide (NaOH). The intercept at the midpoint of the titration, i.e. the point at which 0.5 molar equivalents of base have been added, is numerically equal to the pKa of the acid.

A procedure for determining pKa for a known weak acid is as follows:

The following materials are needed: a sample of pure acid for which pKa is to be determined; CO_2 -free deionized distilled water (prepared by boiling deionized distilled water for 5 minutes); Commercial 0.1N NaOH volumetric standard, certified to 0.1005-0.0995 N, eg. Fisher Scientific SS276; 100-ml calibrated glass burette; 125-ml Erlenmeyer flask pH meter, e.g. Corning Model 140 with standard combination electrode for pH; pH buffers, pH 4.00, 7.00, and 10.00, certified to ±0.01 pH unit at 25, e.g. Fisher Scientific SB101, SB107, and SB115 magnetic stirrer.

All glassware and equipment must be clean and acid-washed if necessary. At least 50 ml of a 0.1 Normal solution of the acid for which the pKa is to be determined is prepared in CO_2-free distilled water. Avoid introducing CO_2 to the solution by avoiding excessive shaking. The final solution is capped until use. The pH meter is calibrated using three buffers at pH 7.00, 3.00, and 10.00, according to the pH meter manufacturer's instructions. The electrode is rinsed with distilled water between samples. The burette is filled with a 0.1 N NaOH standard solution. 50.0 ml of 0.1 N acid solution is added to a 125-ml Erlenmeyer and a stirring bar added.

The pH electrode is inserted into the acid solution and positioned and secured so that it does not interfere with the stirring bar. The initial pH is recorded. Gentle stirring is begun such that the pH reading is not affected. The burette is positioned over the flask to allow incremental addition of the 0.1 N standard NaOH to the 0.1 N acid solution. The initial pH is verified and incremental addition of the base begun. The volumes of base added and the resulting pH readings are recorded. The aim is to record pH changes of 0.2 to 0.3 units or volume increases of about 5ml, whichever comes first. Incremental additions are continued until at least 60 ml of the base have been added and the steep change in pH levels off.

The data is plotted with the volume of base as the x-axis and pH as the y-axis. The points observed are plotted and a smooth line drawn through them. The volume of base added to obtain the equivalence point is determined, i.e. the volume at which one normal-equivalent of base has been added and the acid has been completely neutralised. When the steep portion of the curve is vertical, the equivalence point volume corresponds to the volume of base at the vertical portion of the curve. If the steep portion of the curve is not vertical, the equivalence point can be obtained by locating the volumes of the base at the two end points that bracket the steep change in pH. The mean of the two volumes is the equivalence point.

To determine the pKa, first locate the midpoint of the titration by halving (i.e. ÷2) the volume of base at equivalence point. The midpoint of the titration is the point at which 0.5 normal-equivalents of base have been added, and the acid has been one-half (50%) neutralised. The pH corresponding to the midpoint of the titration is the pK_a of the acid. This is the pH at which 50% of the acid has been neutralised, that is, the molecule exists 50% in the non-ionised form and 50% as the anion.

Examples of suitable weak carboxylic acids include but are not limited to: alpha- or beta-hydroxyacids, dicarboxylic acids, tricarboxylic acids, ascorbic acid, oxamic acid and mixtures thereof. Preferred carboxylic acids, due to their anti-ageing efficacy, are:

ACID	pKa
glycolic	3.8
lactic	3.8
malic	3.4
beta-hydroxybutyric	4.7
acetic	4.75
succinic	4.2
citric	3.1
ascorbic	4.1
salicylic	3.0
oxamic	2.4

and mixtures thereof.

The amount of weak acid in the inventive composition ranges from 0.01 to 20, preferably from 1 to 15 and most preferably from 2 to 12, by weight of the composition. At concentrations below 2% of the acid, there is minimal stinging and the anti-ageing efficacy does not increase significantly above 12%.

It is to be understood that depending on the pH of the composition, the acid may be present as a salt, e.g. an ammonium, potassium or sodium salt.

Although the compositions employed in the inventive method may have any pH in the general range of 2.5 to 10, the inventive methods are particularly useful in compositions having an acidic pH, preferably 3-6 and most

preferably at a pH of 3-5, because such compositions, although efficacious, are particularly irritating.

The compositions employed in the invention comprise a cosmetically acceptable vehicle to act as a diluant, dispersant or carrier for weak carboxylic acid and PEG, so as to facilitate their distribution when the composition is applied to the skin.

The vehicle may be aqueous or an emulsion. Water when present will be in amounts which may range from 5 to 99%, preferably from 40 to 90%, optimally from 50 and 85% by weight.

According to the present invention, the vehicle is preferably at least 50 wt.% water by weight of the vehicle. The compositions are preferably oil-water emulsions, in order to improve dermal delivery of hydroxy acids (See *Sah et al. in J. Cosmet. Sci. 49, 257-273, 1998*). Such improved delivery is frequently accompanied by increased irritation/sting, making the use of PEG in such emulsions particularly critical. In the preferred oil-in-water emulsions according to the present invention, water comprises at least 50 wt.% of the inventive emulsion, most preferably from 50 to 85 wt.%, by weight of the composition.

Besides water, relatively volatile solvents may also serve as carriers within compositions employed in the

present invention. Most preferred are monohydric C_1-C_3 alkanols. These include ethyl alcohol, methyl alcohol and isopropyl alcohol. The amount of monohydric alkanol may range from 1 to 70%, preferably from 10 to 50%, optimally between 15 and 40% by weight.

Emollient materials may also serve as cosmetically acceptable carriers. These may be in the form of silicone oils and synthetic esters. Amounts of the emollients if present may range anywhere from 0.1 to 50%, preferably between 1 and 20% by weight.

Silicone oils may be divided into the volatile and non-volatile variety. The term "volatile" as used herein refers to those materials which have a measurable vapour pressure at ambient temperature. Volatile silicone oils are preferably chosen from cyclic or linear polydimethylsiloxanes containing from 3 to 9, preferably from 4 to 5, silicon atoms. Linear volatile silicone materials generally have viscosities less than about 5 centistokes at 25°C while cyclic materials typically have viscosities of less than about 10 centistokes.

Nonvolatile silicone oils useful as an emollient material include polyalkyl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers. The essentially non-volatile polyalkyl siloxanes useful herein include, for example, polydimethyl siloxanes with viscosities of from about 5 to about 25 million centistokes at 25°C. Among

the preferred non-volatile emollients useful in the present compositions are the polydimethyl siloxanes having viscosities from about 10 to about 400 centistokes at 25°C.

Among the suitable emollients are:

(1) Alkenyl or alkyl esters of fatty acids having from10 to 20 carbon atoms. Examples thereof include isoarachidyl neopentanoate, isononyl isonanonoate, oleyl myristate, oleyl stearate, and oleyl oleate.

(2) Ether-esters such as fatty acid esters of ethoxylated fatty alcohols.

(3) Polyhydric alcohol esters. Ethylene glycol mono and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (200-6000) mono- and di-fatty acid esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid

ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters are satisfactory polyhydric alcohol esters.

(4) Wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate and arachidyl behenate.

(5) Sterols esters, of which cholesterol fatty acid esters are examples thereof.

Fatty acids having from 10 to 30 carbon atoms may also be included as cosmetically acceptable carriers for compositions of this invention. Illustrative of this category are pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidic, behenic and erucic acids.

Thickeners may also be utilised as part of the cosmetically acceptable carrier of compositions according to the present invention. Typical thickeners include crosslinked acrylates (e.g. Carbopol 982), hydrophobically-modified acrylates (e.g. Carbopol 1382), cellulosic derivatives and natural gums. Among useful cellulosic derivatives are sodium carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose and hydroxymethyl cellulose. Natural gums suitable for the present invention include guar, xanthan, sclerotium, carrageenan,

pectin and combinations of these gums. Amounts of the thickener may range from 0.0001 to 5%, usually from 0.001 to 1%, optimally from 0.01 to 0.5% by weight.

Collectively, the water, solvents, silicones, esters, fatty acids, and/or thickeners will constitute the cosmetically acceptable carrier in amounts from 1 to 99.9%, preferably from 80 to 99% by weight.

An oil or oily material may be present, together with an emulsifier to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophilic-lipophilic balance (HLB) of the emulsifier employed.

Surfactants may also be present in cosmetic compositions of the present invention. Total concentration of the surfactant will range from 0.1 to 40%, preferably from 1 to 20%, optimally from 1 to 5% by weight of the composition. The surfactant may be selected from the group consisting of anionic, nonionic, cationic and amphoteric surfactants. Particularly preferred nonionic surfactants are those with a C_{10}-C_{20} fatty alcohol or acid hydrophobe condensed with from 2 to 100 moles of ethylene oxide or propylene oxide per mole of hydrophobe; C_2-C_{10} alkyl phenols condensed with from 2 to 20 moles of alkylene oxide; mono- and di- fatty acid esters of ethylene glycol; fatty acid monoglyceride; sorbitan, mono- and di- C_8-C_{20} fatty acids; block copolymers

(ethylene oxide/propylene oxide); and polyoxyethylene sorbitan as well as combinations thereof. Alkyl polyglycosides and saccharide fatty amides (e.g. methyl gluconamides) are also suitable nonionic surfactants.

Preferred anionic surfactants include soap, alkyl ether sulfate and sulfonates, alkyl sulfates and sulfonates, alkylbenzene sulfonates, alkyl and dialkyl sulfosuccinates, C_8-C_{20} acyl isethionates, acyl glutamates, C_8-C_{20} alkyl ether phosphates and combinations thereof.

Various types of additional active ingredients may be present in cosmetic compositions of the present invention. Actives are defined as skin benefit agents other than emollients and other than ingredients that merely improve the physical characteristics of the composition. Although not limited to this category, general examples include additional anti-sebum ingredients and sunscreens.

Sunscreens include those materials commonly employed to block ultraviolet light. Illustrative compounds are the derivatives of PABA, cinnamate and salicylate. For example, avobenzophenone (Parsol 1789®) octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone (also known as oxybenzone) can be used. Octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone are commercially available under the trademarks, Parsol MCX

and Benzophenone-3, respectively. The exact amount of sunscreen employed in the compositions can vary depending upon the degree of protection desired from the sun's UV radiation.

Many cosmetic compositions, especially those containing water, must be protected against the growth of potentially harmful microorganisms. Preservatives are, therefore, necessary. Suitable preservatives include alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, propionate salts, and a variety of quaternary ammonium compounds. Particularly preferred preservatives of this invention are methyl paraben, propyl paraben, phenoxyethanol and benzyl alcohol. Preservatives will usually be employed in amounts ranging from about 0.1% to 2% by weight of the composition.

The composition employed in the invention is intended primarily as a product for topical application to human skin, especially as an agent to improve the appearance of aged or photoaged skin.

In use, a quantity of the composition, for example from 1 to 100 ml, is applied to exposed areas of the skin, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the skin using the hand or fingers or a suitable device.

The following specific examples further illustrate the invention, but the invention is not limited thereto.

List of suppliers

Active Ingredient	Supplier
Polyethylene Glycol	Sigma, Union Carbide Corp.
Arabinogalactan	Larex, Inc.
Glycolic acid	DuPont
Lactic acid	Purac America, Inc.
Hydrocortisone(water soluble)	Sigma

EXAMPLE 1

This example measured sting caused by formulations containing glycolic acid.

Procedure for in-vivo sting test: This was a randomized, double blind study where each subject evaluated one test formulation and a control formulation or two test formulations on contralateral nasolabial folds. During the qualification phase, each subject evaluated an 8% glycolic acid test versus a vehicle control (0% glycolic). Subjects with established left/right balanced sensitivity to glycolic acid were qualified. A maximum of 20 qualified subjects (minimum of 15) were utilized in each subsequent test. One paired comparison was made on each testing day, with a minimum of 3 days between sting testing throughout the study. Subjects underwent a 15 second Ivory soap wash regime immediately

prior to product testing for enhancing sting response. Any subjects experiencing any stinging/burning on the test sites immediately prior to product application did not have products applied. Study personnel then applied one test formulation and one control or test formulation simultaneously to the appropriate left/right test site, and gently but thoroughly rubbed in. Subjects compared the stinging potential of the two formulations, over a 7.5 minute period using a self-assessment questionnaire.

Sting/Burn Propensity: The degree of stinging/burning felt on the left and right inner cheek and crease of the nose was evaluated using the following scale at the times indicated in the Tables below:

0 -no stinging / burning; 1 -very slight stinging / burning; 2 -slight stinging / burning; 3 - moderate stinging / burning; 4 -moderately high stinging / burning; 5 -high stinging / burning; 6 -extreme stinging / burning.

Determination of Statistical Significance: At each evaluation time point after baseline, the parametric paired t-test (two-tailed) was performed, to compare the extent of attribute change from baseline between each treatment comprising a paired comparison test, with subject acting as a block in these analyses. (Ref. *Statistical Methods*, Snedecor and Cochran, Iowa State University Press, 7th Edition, 1980, pp. 84-86]). The

test can be implemented using the SAS software procedure MEANS with the T and PRT options specified.

Forced choice for stinging/burning: At each evaluation point (0,2.5,5.0 and 7.5 min), the response to the forced choice assessment "Which side of the face has more stinging?" was analysed as follows: the number of subjects choosing treatment A was compared to the number of subjects choosing treatment B using a parametric paired t-test (2-tailed). Statistical significance was determined at $p \leq 0.1$. Results from several paired comparisons using this assessment method are shown (see later) in Tables 1B, 2B, 3B, 4B, and 5B.

An oil-in-water emulsion cream (Base Formula A) was prepared:

FULL CHEMICAL NAME OR CTFA NAME	% ACTIVE LEVEL IN FORMULATION	TRADE NAME AND % ACTIVE AS RECEIVED
Water, DI	46.54	
Disodium EDTA	0.05	Sequesterene Na2
Magnesium aluminum silicate	0.6	Veegum Ultra
Methyl paraben	0.15	Methyl Paraben
Simethicone	0.01	DC Antifoam Emulsion
Butylene glycol 1,3	3.0	Butylene Glycol 1,3
Hydroxyethylcellulose	0.5	Natrosol 250HHR
Glycerine, USP	2.0	Glycerine USP
Xanthan gum	0.2	Keltrol 1000
Triethanolamine	1.2	Triethanolamine 99%
Stearic acid	3.0	Pristerene 4911
Propyl paraben NF	0.1	Propylparaben NF
Glyceryl hydrostearate	1.5	Naturechem GMHS
Stearyl alcohol	1.5	Lanette 18DEO
Isostearyl palmitate	6.0	Protachem ISP
C12-15 alcohols octanoate	3.0	Hetester FAO
Dimethicone	1.0	Silicone Fluid 200(50cts)
Cholesterol NF	0.5	Cholesterol NF
Sorbitan stearate	1.0	Sorbitan Stearate
Butylated hydroxytoluene	0.05	Embanox BHT
Tocopheryl acetate	0.1	Vitamine E Acetate
PEG-100 stearate	2.0	MYRJ 59
Sodium stearoyl lactylate	0.5	Pationic SSL
Water, DI	q.s.	

*Unless otherwise noted, active levels were approximately 100%.

The sting/burn of Base Formula A with or without 8% glycolic acid was tested using the in-vivo sting test. *The results obtained are summarised in Tables 1A and 1B:*

Table 1A
Sting/Burn Propensity

Mean Degree of Stinging/Burning (0-6 Scale)	Base Formula A (pH 7.2)	Base Formula A +8% Glycolic Acid (pH 3.8)
Immediately after application	0.05	1.05 *
2.5 minutes after Application	0.25	1.85 *
5.0 minutes after Application	0.25	2.00 *
7.5 minutes after Application	0.35	2.15 *

* $p < 0.05$

Table 1B

Forced Choice for Stinging/Burning: Which side is worse?
Results 7.5 minutes after application

	Base Formula A (pH 7.2)	Base +8% Glycolic Acid (pH 3.8)
Number of Subjects Indicating more Discomfort (sting/burn)	0	20

* $p < 0.05$

The sting/burn propensity of glycolic at 8% and 4% level were compared. The results obtained are summarised in Table 1C.

Table 1C
Sting/Burn Propensity

Mean Degree of Stinging/Burning (0-6 Scale)	Base Formula A+ 4% Glycolic Acid (pH 3.8)	Base Formula A+8% Glycolic Acid (pH 3.8)
Immediately after application	0.45	1.35 *
2.5 minutes after Application	0.60	1.75 *
5.0 minutes after Application	0.60	1.95 *
7.5 minutes after Application	0.55	1.65 *

* $p < 0.05$

It can be seen from the results in Tables 1A-1C that 8% glycolic acid at pH 3.8 is significantly more stinging than either the base formulation or 4% glycolic acid. Although stinging can be reduced by increasing pH or lowering the active level, such changes in composition significantly affect dermal delivery and, consequently, the efficacy of the active.

EXAMPLE 2

This example measured the effect of PEG 200D on glycolic acid sting at pH 3.8 in Base Formula A. The in-vivo

sting test and Base Formula A are described in Example 1.

Base Formula A was prepared without the glycolic acid, base, and PEG. The PEG was solubilised in a separate beaker containing glycolic acid + base (ammonium hydroxide) and a small level of water from the formulation (no more than 5% is needed) - thus, the original Base Formula A was originally made with 5% less water. The glycolic acid/PEG solution was then post added to the Base Formula A during the cool down stage (usually at a temperature of about 45°C). The results obtained are summarised in Tables 2A and 2B.

Table 2A.
Sting/Burn propensity

Mean Degree of Stinging/Burning (0-6 Scale)	Base Formula A + 8% Glycolic +5% PEG 200D (pH 3.8)	Base Formula A + 8% Glycolic (pH 3.8)
Immediately after application	0.21	0.53
2.5 minutes after Application	0.58	1.16 *
5.0 minutes after Application	0.53	1.0
7.5 minutes after Application	0.47	0.84

* $p < 0.1$

Table 2B
Forced Choice for Stinging/Burning; Which side is worse?
Results 7.5 minutes after application

	Base Formula A + 8% Glycolic +5% PEG 200D (pH 3.8)	Base Formula A + 8% Glycolic (pH 3.8)
Number of Subjects Indicating more Discomfort (sting/burn)	6	13

It can be seen from the results in Tables 2A and 2B that PEG 200D significantly reduced the stinging/burning propensity of Base Formula A containing 8% glycolic acid.

EXAMPLE 3

This example measured the effect of PEG 8000D on glycolic acid sting at pH 3.8 in Base Formula A. The in-vivo sting test and Base Formula A are described in Example 1. The results obtained are summarised in Tables 3A, 3B, and 3C.

Table 3A
Sting/Burn propensity

Mean Degree of Stinging/Burning (0-6 Scale)	Base Formula A + 8% Glycolic +5% PEG 8KD (pH 3.8)	Base Formula A + 8% Glycolic (pH 3.8)
Immediately after application	0.27	1.0 *
2.5 minutes after Application	0.47	1.2 *
5.0 minutes after Application	0.40	0.93
7.5 minutes after Application	0.27	0.73

* p < 0.1

Table 3B
Forced Choice for Stinging/Burning; Which side is worse?
Results: 0 minutes (immediately) after application

	Base Formula A + 8% Glycolic +5% PEG 200D (pH 3.8)	Base Formula A + 8% Glycolic (pH 3.8)
Number of Subjects Indicating more Discomfort (sting/burn)	2	8 *

* p<0.1

Table 3C
Sting/Burn propensity

Mean Degree of Stinging/Burning (0-6 Scale)	Base Formula A + 8% Glycolic +5% PEG 8KD (pH 3.8)	Base Formula A + 4% Glycolic Acid (pH 3.8)
Immediately after application	0.20	0.27
2.5 minutes after Application	0.40	0.80
5.0 minutes after Application	0.20	0.53
7.5 minutes after Application	0.07	0.47 *

*p<0.1

It can be seen from the results in Tables 3A and 3B that PEG 8KD significantly reduced the stinging/burning propensity of Base Formula A containing 8% glycolic acid. In Table 3C, the stinging response of Base +8% glycolic + 5% PEG 8KD was less than that of Base + 4% glycolic, significant at 7.5 minutes after application. Thus, it is concluded that addition of 5% PEG 8KD reduced the sting of the formulation containing 8% glycolic acid to less than that of a formulation containing only 4% glycolic acid.

EXAMPLE 4

This example tested the effect of PEG 11KD on glycolic acid sting in a lotion. The test is described in Example

1. The oil-in-water lotion (Base Formula B) was prepared having the following formula:

FULL CHEMICAL NAME OR CTFA NAME	% ACTIVE LEVEL IN FORMULATION	TRADE NAME AND % ACTIVE AS RECEIVED
Magnesium Aluminum Silicate	0.550	Veegum Ultra
1,3 Butylene glycol	2.4	butyleneglycol
Disodium EDTA	0.05	Clewat-N
Xanthan Gum	0.15	Keltrol
Decaglyceryl monolaurate	2.0	Nikkol Decaglyn 1-L
Glycerin	8.0	Maruko RG
Triethanolamine	2.0	TEA (99%)
Methyl Paraben	0.195	methyl paraben
Propyl paraben	0.05	propyl paraben
Sodium Isostearoyl Lactylate	0.1	Pationic ISL
Sodium carboxymethylcellulose	0.15	Cellulose gum 9H4XF
Ethyl Oleate	0.6	Nofable EO-90
Squalane	2.0	Nikkol Squalane
Glyceryl Tri (2-Ethylhexanoate)	3.6	Panaceat 800B
Liquid Petrolatum	5.8	Carnation Min Oil
Stearic Acid	0.3	Pristerene 4911
Cetostearyl Alcohol	0.5	Conol 30RC
Butyl paraben	0.05	Butyl paraben

Hydrogenated Soybean phospholipid	0.075	Basis LP-20H (20-30%)
Cholesterol	0.05	cholesterol
dl-alpha tocopherol linoleate/oleate	0.05	Vitamin E linoleate mixture
Dibutylhydroxy toluene	0.05	BHT
Glycolic acid	2.80	Glypure 70 (70%)
Glycolic acid/Ammonium hydroxide solution	5.08	GA Mixture NL (82.6%)
4-tertbutyl-4-methoxydibenzoylmethane	0.1	Parsol 1789
Ethylhexyl 4-methoxycinnamate	0.1	Parsol MCX
Di-(2-octyldodecyl)-N-lauroyl-L-glutamate	0.2	Amiter LG-OD
3-methyl-1,3-butanediol	1.6	Isopreneglycol
Polyacrylamide/C13-14 Isoparrafin/Laureth 7	1.0	Sepigel 305
Glucose cetostearate / cetostearyl alcohol	0.5	Montanov 68
Ammonium Hydroxide to pH 3.8	0-2.0	Ammonium hydroxide
Fragrance	0.098	Fleur J412225 QUT
Deionized Water	to 100% (59.8%)	Deionized water

*Unless otherwise noted, active levels are approximately 100%.

The emulsion concentrate was made using all ingredients except glycolic / base / PEG and without all the water.

In a separate beaker glycolic + base + PEG + about 5% of the total water was combined and mixed until the PEG solubilises completely. This mixture was then post added to the emulsion. The pH was then adjusted to the correct pH using base, and then the remainder of the water was added to qs. 100%.

The results obtained are summarised in Tables 4A and 4B

Table 4A
Sting/Burn propensity

Mean Degree of Stinging/ Burning (0-6 Scale)	Base Lotion B + 8% Glycolic +5% PEG 11KD (pH 3.8)	Base Lotion B + 8% Glycolic (pH 3.8)
Immediately after application	0.55	0.55
2.5 minutes after Application	1.28	1.89 *
5.0 minutes after Application	1.33	1.78
7.5 minutes after Application	1.39	1.67

* $p<0.1$

Table 4B
Forced Choice for Stinging/Burning; Which side is worse?
Results 2.5 minutes after application

	Base Lotion B + 8% Glycolic + 5% PEG 11KD (pH 3.8)	Base Lotion B + 8% Glycolic (pH 3.8)
Number of Subjects Indicating more Discomfort (sting/burn)	4	14 *

* $p<0.1$

It can be seen from the results in Tables 4A and 4B that PEG 11KD reduced the stinging/burning propensity of Base Formula B containing 8% glycolic acid.

EXAMPLE 5

PEG 8KD was tested for its ability to reduce sting in an additional cream base containing 4% glycolic acid at pH 4.2. The test procedure is described in Example 1. Base Formula C was as follows:

FULL CHEMICAL NAME OR CTFA NAME	% ACTIVE LEVEL IN FORMULATION
Magnesium Aluminum Silicate	0.3
Disodium EDTA	0.05
Methyl hydroxybenzoate	0.15
1,3- Butyleneglycol	3.0
Xanthan Gum	0.2
Hydroxyethyl cellulose	0.25
Glycerin Concentrated	2.0
Triethanolamine	1.2
Sodium Isostearoyl lactate	0.5
Glyceryl monostearate	1.5
Sorbitan Monostearate	1.0
Polyethyleneglycol monostearate (150 EO)	1.09
Polyethyleneglycol monostearate (40 EO)	0.910
Stearyl Alcohol	1.5
Stearic Acid	2.0
Isostearyl Palmitate	6.0
Isocetyl Octanoate	3.0
Methyl Polysiloxane	1.0
Cholesterol	0.5
Dibutylhydroxytoluene	0.05
Propyl Parahydroxybenzoate	0.1
dl-Tocopheryl Acetate	0.1
Glycolic acid	5.7

Potassium Hydroxide	1.1
Fragrance	0.09
DI Water (to 100)	66.710

The results obtained are summarised in Tables 5A and 5B

Table 5A
Sting/Burn propensity

Mean Degree of Stinging/ Burning (0-6 Scale)	Base Formula C + 4% Glycolic + 5% PEG 8KD (pH 4.2)	Base Formula C +4% Glycolic (pH 4.2)
Immediately after application	0.17	0.56 *
2.5 minutes after Application	0.72	1.22
5.0 minutes after Application	0.72	1.33 *
7.5 minutes after Application	0.61	1.17 *

*p<0.1

Table 5B

Forced Choice for Stinging/Burning; Which side is worse?
Results 2.5 minutes after application

	Base Lotion C + 4% Glycolic + 5% PEG 8KD (pH 4.2)	Base Lotion B + 4% Glycolic (pH 4.2)
Number of Subjects Indicating more Discomfort (sting/burn)	5	11 *

* p<0.1

COMPARATIVE EXAMPLE 6

This example tested the various compounds for their ability to reduce sting. The test procedure and Base Formula A are described in Example 1. The results obtained are summarised in Tables 6A and 6B.

Table 6A
Hydrocortisone

Mean Degree of Stinging/ Burning (0-6 Scale)	Base Formula A + 8% Glycolic + 0.1% Hydrocortisone (pH 3.8)	Base Formula A + 8% Glycolic (pH 3.8)
Immediately after application	0.94	0.76
2.5 minutes after Application	0.68	0.58
5.0 minutes after Application	0.36	0.36
7.5 minutes after Application	0.21	0.21

Table 6B
Arabinogalactan

Mean Degree of Stinging/Burning (0-6 Scale)	Base + 8% Glycolic + 5% Arabinogalactan (pH 3.8)	Base +8% Glycolic Acid (pH 3.8)
Immediately after application	0.89	0.47
2.5 minutes after Application	1.0	0.78
5.0 minutes after Application	0.89	0.63
7.5 minutes after Application	0.63	0.52

The results in Tables 6A and 6B demonstrate that neither hydrocortisone nor arabinogalactan reduced the sting. In fact, addition of 5% arabinogalactan (Table 6B) slightly enhanced the sting of the anti-ageing cream.

EXAMPLE 7

This example tested the effect of polyethylene glycol on the delivery of glycolic acid molecules to the skin layers.

Procedure: Dermal delivery of actives was measured by the in-vitro percutaneous absorption (PCA) test. The tests were carried out using dermatomed pig skin and Bronaugh flow-through cells 3-4 week old female dorsal pig skin, rinsed with water only was obtained from Buckshire Farms. The skins were stored at -70°C until

use. They were thawed at room temperature, shaved gently with a Norelco electric shaver, sliced to 510 um thickness using a Padgett Dermatome, punched into 18-mm discs with a cork borer, and mounted in Bronaugh diffusion cells over 37°C, pH 7.1 Hank's balanced salts buffer flowing at 5 ml/min. After 30 min equilibration, transepidermal water loss was determined using a ServoMed EP1 evaporimeter. Skin discs allowing water losses of >5 g/m2 per hr were replaced. The skin discs were dosed with 2 μL of product containing the nonlabelled active plus an insignificant weight of the active radiolabelled with 3H or 14C at about 30 microCurie/gram product. The dose was delivered via a displaced volume pipette and spread on the 9-mm diameter exposed skin surface with either a latex finger cot stretched over a cotton tip applicator. Contact times were 6 hours, with receptor fluid being sampled at either 1- or 2-hour intervals in scintillation vials. At the end point, the skin surface was rinsed with three~1-ml aliquots of water, the skin discs were removed from the apparatus, and blotted with 1/3 of tissue paper (Kim Wipe). The upper surface was tape-stripped 9 times with Scotch transparent tape to obtain the stratum corneum, and the epidermis was separated from the dermis with a scalpel. Analysis by liquid scintillation spectrometry included all samples necessary to account for complete balance and recovery of the radiolabelled material, including product retained on the applicator during delivery, the water-rinsed and excess removed on

the tissue, tape stripped stratum corneum, epidermis, dermis (counted after NCS digestion), receptor fluid, the empty Bronaugh cells, filter papers, and rinse pipettes. Theoretical applied dose was determined by subtracting the material retained on the applicator from the mean measured radioactivity of a minimum of six weighed 2-μL aliquots of the radiolabelled test product. Data were reported as percent-of-dose in tissue fractions. A p -value of ≤ 0.1 was considered statistically significant.

Polyethylene glycol effect on delivery was tested for Base Formula A with molecular weight of 200D and 8KD.

The results obtained are summarised in Tables 7A and 7B.

Table 7A

Skin Tissue	Base Formula A+8% glycolic acid; pH=3.8	Base Formula A+8% glycolic acid+5% PEG 200D; pH=3.8
Stratum Corneum	5.4	7.1
Epidermis+Dermis	5.2	4.2
Receptor Fluid	1.2	0.9
Total	11.8	12.2

Table 7B

Skin Tissue	Base Formula A +8% glycolic acid; pH=3.8	Base Formula A+8% glycolic acid+5% PEG 8KD; pH=3.8
Stratum Corneum	4.6	5.0
Epidermis+Dermis	3.8	3.7
Receptor Fluid	7.5	4.0
Total	15.9	12.7

It can be seen from the results in Tables 7A and 7B that the addition of 5% polyethylene glycol did not adversely affect the delivery of glycolic acid to different skin tissue layers. In fact, the presence of PEG led to a directional increase in the combined delivery of glycolic acid to skin tissues (corneum, epidermis and dermis)

Thus, the results of Examples 1 - 5 demonstrate that polyethylene glycol reduced the sting caused by weak acids. Other known anti-irritants, such as hydrocortisone, as well as a polysaccharide, arabinogalactan, did not reduce the sting caused by weak carboxylic acids (Comparative Example 6). Unlike numerous prior art approaches, the addition of PEG did not adversely affect the delivery of actives to skin layers (Example 7).

EXAMPLE 8

Example 8 illustrates topical compositions according to the present invention. The compositions can be processed in a conventional manner and are suitable for cosmetic use. In particular, the compositions are suitable for application to aged and/or UV-damaged skin to improve the appearance and the feel thereof as well as for application to healthy skin to prevent or retard deterioration thereof.

A typical oil-in-water emulsion within the scope of the invention is as follows:

Chemical name	wt.%
PEG 10KD	4
glycolic acid	7
propylene glycol	1
glycerin	1
hydroxyethylcellulose	0.5
magnesium aluminum silicate	0.5
imidazolidinyl urea	0.5
tetrasodium EDTA	0.05
petrolatum	2
isopropyl palmitate	5
dimethicone	0.5
cholesterol	0.5
cetyl alcohol	0.5
isostearic acid	3
peg-40 stearate	1
peg-100 stearate	1
sorbitan stearate	1
ammonium hydroxide	to pH 4.0
water DI	qs to 100%

Another typical oil-in-water emulsion within the scope of the invention is as follows:

Chemical name	wt.%
Polyethylene Glycol 40KD	5
glycolic acid	10
propylene glycol	1
hydroxyethylcellulose	0.5
magnesium aluminum silicate	0.5
imidazolidinyl urea	0.2
petrolatum	2
isopropyl palmitate	5
dimethicone	0.5
cholesterol	0.5
stearic acid	3
isostearic acid	1.5
glycerol stearate	1.5
peg-40 stearate	1
peg-100 stearate	1
sorbitan stearate	1
cetyl alcohol	0.5
ammonium hydroxide	to pH 3.8
water DI	qs to 100%

A typical water-in-oil dispersion within the scope of the invention is as follows:

Chemical name	wt.%
isostearyl neopentanoate	20
peg-8 caprylic/capric glycerides	6
cetyl octanoate	17
polyglyceryl-6 dioleate	15
cyclomethicone	20
glyceryl isostearate	0.5
isostearic acid	0.5
ceramide III	0.1
ppg-5-cetheth-20	3
L-lactic acid/potassium lactate	6
hydroxycaprylic acid	0.1
water DI (to 100)	1.3
Polyethylene Glycol 200D	10

The following oil-in-water emulsion within the scope of the invention is prepared:

Chemical name	wt.%
xanthan gum	0.2
disodium EDT	0.1
sodium PCA	0.5
diazodinyl urea	0.3
titanium dioxide	1
stearic acid	3
cyclomethicone	0.3
cetyl alcohol	0.5
glyceryl stearate	0.5
peg-100 stearate	0.5
steareth-2	0.2
lecithin	0.5
tocopherol	0.2
octyl methoxycinnamate	6
polyethylene glycol 20KD	6
glycolic acid	3
malic acid	2
lactic acid	2
triethanolamine	to pH 3.8
water DI	qs to 100%

It should be understood that the specific forms of the invention herein illustrated and described are intended to be representative only. Changes, including but not limited to those suggested in this specification, may be made in the illustrated embodiments without departing from the clear teachings of the disclosure. Accordingly, reference should be made to the following appended claims in determining the full scope of the invention.

CLAIMS:

1. A method of reducing skin irritation or sting from a weak carboxylic acid, the method comprising topically applying a composition comprising the weak carboxylic acid and polyethylene glycol in a cosmetically acceptable vehicle.

2. A method according to claim 1 wherein the weak carboxylic acid has pKa of above about 2.

3. A method according to claim 2, wherein the acid is glycolic acid, lactic acid, malic acid, beta hydroxybutyric acid, acetic acid, succinic acid, citric acid, ascorbic acid, salicylic acid or oxamic acid, or mixtures thereof.

4. A method according to any one of the preceding claims, wherein the pH of the composition is in the range of from 3 to 6.

5. A method according to any one of the preceding claims wherein the molecular weight of polyethylene glycol is from 200D to 20,000D.

6. A method according any one of the preceding claims wherein the amount of polyethylene glycol is from 0.1 to 20 wt.%.

7. A method according to any one of the preceding claims wherein the composition is an oil-in-water emulsion.

8. A method according to any one of the preceding claims wherein the method is carried out at pH 2.5 to 10.

9. A method according to claim 8 wherein the method is carried out at pH 3-6.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 5 925 679 A (MATHER KAMRAN ET AL) 20 July 1999 (1999-07-20) abstract column 1, line 20 - line 33 column 2, line 25 - line 34 column 2, line 48 - line 50 column 2, line 66 -column 3, line 42 table 1 example 5 column 5, line 41 - line 53 claims ---	1,2,4,5, 7-9 1-3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07303

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